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Point/Counterpoint

Point: There is a need for supplemental XRT with brachytherapy in the treatment of intermediate-risk prostate cancer patients

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One of the critical elements that have led to improved outcomes for intermediate-risk prostate cancer patients is the use of dose escalation (1–7). A meta-analysis of the seven randomized dose-escalated trials has demonstrated a biochemical control benefit for intermediate-risk patients with increasing biologically effective doses (BEDs) (5). Viani *et al.* found that a near linear benefit was evident with escalation of the radiation dose, and there was no sign that the dose effect had reached a plateau with further escalation of the radiation dose; these studies included BED of up to 175 Gy. In addition, Levegrun *et al.* (8) have used posttreatment biopsies to represent local control and suggested a TCP50 of 70.5 Gy (BED of 155 Gy) and near linear tumor control improvements with doses approaching 85 Gy (BED of 187 Gy). Current therapy for intermediate-risk patients with dose-escalated external beam radiation therapy (EBRT) plus androgen deprivation therapy (9, 10) result in 10-year actuarial biochemical failure rates of 20–25% and local failure rates of 15–25% (11, 12). As seen in Table 1, most brachytherapy implant alone series result in 10-year actuarial biochemical failure rates of greater than 20% for intermediate-risk patients. Clearly, intermediate-risk prostate cancer is not uniformly eradicated with BEDs of brachytherapy implant or dose-escalated EBRT alone (BED of 150–190 Gy) and warrants more aggressive therapy.

Supplemental EBRT is one of the most reliable and consistent ways for safely escalating radiation dose levels in conjunction with brachytherapy to facilitate the delivery of higher BED levels within the prostate and the extraprostatic tissue. Using BED models published by Stock *et al.* (13) (using α/β of 2.0), ^{125}I monotherapy implant prescription of 144 Gy has a BED of approximately 160 Gy based on the D_{90} coverage; however, combination therapy with 110 Gy of ^{125}I implant and 50.4 Gy of supplementary EBRT yields a BED of approximately 230 Gy. This marked difference in BED has been shown to correlate with improved biochemical and local control. Stone *et al.* (14) reported that intermediate-risk patients had a positive post-treatment biopsy rate of 14% when treated with a BED <150 Gy and only 5.3% biopsy positivity for BED >200 Gy. Importantly, residual disease post-EBRT has been shown to predict for both distant metastases and prostate cancer–related mortality (12). Furthermore, a multi-institutional study of intermediate- and high-risk patients demonstrated that a BED >220 Gy resulted in significantly improved freedom from biochemical failure, a dose not readily achieved by brachytherapy implant alone.

Beyond intraprostatic dose escalation, another important and recognized advantage of supplemental EBRT is the ability to cover extraprostatic disease for extracapsular extension (ECE), seminal vesicle invasion (SVI), and even lymph node involvement (Table 2). Based on original Partin data using the Roach formula, even low-risk patients can have >40% risk of having ECE at time of radical prostatectomy (15). To complicate this issue further, standard hematoxylin and eosin (H & E) staining has been shown to underestimate the presence of ECE, which has been confirmed by molecular studies (16). Multiple series have demonstrated that ECE commonly extends up to 5 mm radially from the prostate, with maximum tumor extension documented ≥10 mm (17, 18). Dosimetric data from Merrick *et al.* (19) have demonstrated that the distance measured radially from the prostate is encompassed by the 100% isodose line at a distance of ≥3 mm from the prostate only 86% of the time and <70% is encompassed when at a distance ≥5 mm from the prostate. Even when analyzing coverage by the 75% isodose line, ~7% of the coverage on average was not encompassed ≥5 mm from the prostate (19). At the edge of the target volume, the dose decreases up to ~20 Gy/mm; thus, if the margin is 3 mm at a point, but ECE extends to 5 mm, a 144-Gy implant may decrease to 100 Gy in the region of ECE. This would represent substantial underdosage of disease and would have the

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Table 1
Summary of long-term biochemical control outcomes by modality

Study	Modality	*n*	Dose	8-year bRFS (%)	10-year bRFS (%)	Notes
Brachytherapy alone						
Hinnen *et al.* (26)	Brachy	369	I125 was 144 Gy		61	
Klein *et al.* (27)	Brachy	204	I125 was 144 Gy	82		
Munro *et al.* (28)	Brachy	187	I125 was 145 Gy		78	
Taira *et al.* (29)	Brachy	144	I125 was 145 Gy Pd103 was 125 Gy		96	
Vassil *et al.* (30)	Brachy	256	I125 was 144 Gy		75*	*Estimated based on KM
Multi-institutional report (31)	Brachy	960	I125 was 144 Gy Pd103 was 130 Gy	61	55*	*Estimated based on KM
Ho *et al.* (32)	Brachy	383	I125 was 160 Gy Pd103 was 124 Gy		76	
Combination brachytherapy plus EBRT						
Critz *et al.* (33)	Combo-RT	447	I125 was 110 Gy EBRT was 45 Gy with boost of 7.5 Gy all in 1.5 Gy/fx		80	Boost to prostate base and seminal vesicles
Dattoli *et al.* (34)	Combo-RT	119	Pd103 was 80–90 Gy EBRT was 39–54 Gy in 1.8 Gy/fx		87	
Ho *et al.* (32)	Combo-RT	175	Pd103 was 100 Gy EBRT was 45 Gy in 1.8 Gy/fx		91	
Merrick *et al.* (35)	Combo-RT	425	I125 was 110 Gy Pd103 was 90 Gy EBRT was 45 Gy in 1.8 Gy/fx		97	80% of patients were combo-RT
Brachytherapy as monotherapy or combination therapy: outcomes not separated by modality						
Bittner *et al.* (36)	Brachy	171	Not specified		97	
	Combo-RT	465	EBRT was 45 Gy in 1.8 Gy/fx			
Burri *et al.* (37)	Brachy	460	I125 was 160 Gy Pd103 was 124 Gy	88		
	Combo-RT	75	Pd103 was 100 Gy EBRT was 45 Gy in 1.8 Gy/fx			
Merrick *et al.* (38)	Brachy	212	I125 was 144 Gy Pd103 was 125 Gy	98		
	Combo-RT		I125 was 110 Gy Pd103 was 90 Gy EBRT was 45 Gy in 1.8 Gy/fx			
Potters *et al.* (39)	Brachy	445	I125 was 144 Gy Pd103 was 136 Gy		76	
	Combo-RT	109	I125 was 108 Gy Pd103 was 102 Gy EBRT was 41.4–45 Gy in 1.8 Gy/fx			
Stone *et al.* (14)	Brachy	141	I125 was 160 Gy Pd103 was 124 Gy		79	
	Combo-RT		Pd103 was 100 Gy EBRT was 45 Gy in 1.8 Gy/fx			
Zelefsky *et al.* (40)	Brachy	553	I125 was 144 Gy Pd103 was 125 Gy		90*	*Estimated based on KM
	Combo-RT		I125 was 110 Gy Pd103 was 100 Gy EBRT was 50.4 in 1.8 Gy/fx			

bRFS = biochemical recurrence-free survival; Brachy = brachytherapy; KM = Kaplan Meier; Combo-RT = combination brachytherapy and external beam radiotherapy; EBRT = external beam radiotherapy.

biologic equivalence of delivering 50.4 Gy using EBRT as monotherapy, a grossly insufficient dose to treat ECE. This concern of monotherapy potentially representing underdosage of disease is clearly illustrated in Fig. 1.

Despite excellent clinical outcomes with combination therapy, one must ask if we are simply *shifting* the therapeutic ratio by increasing tumor control with a concomitant increased risk for toxicity, or if we are actually *improving* the therapeutic ratio. Multiple prospective trials have evaluated the safety of combination therapy. Two randomized Phase 3 trials found slightly differing results regarding the toxicity of combination EBRT and

Table 2
Benefits of supplemental external beam radiotherapy

Dose escalation
Intraprostatic dose escalation
Extracapsular extension ≤5 mm from capsule and proximal seminal vesicles dose escalation
Improved coverage
Ability to cover extracapsular extension >5 mm from prostate
Ability to treat entire seminal vesicles
Ability to treat pelvic lymph nodes
Compensate for an inadequate implant

brachytherapy (6, 7, 20). Hoskin *et al.* (7) reported that combination therapy resulted in similar rates of genitourinary (GU) toxicity but, interestingly, demonstrated decreased rates of acute rectal toxicity with combination therapy. Sathya *et al.* (6) reported a nonsignificant ($p = 0.09$) increase in late GU toxicity with combination therapy over non-dose–escalated EBRT, and no difference in late GI toxicity. Radiation Therapy Oncology Group 0019 was a Phase II multi-institutional trial that used combination EBRT with low dose rate (LDR) brachytherapy and reported that of 138 patients, 4 (2.9%) experienced Grade 3 gastrointestinal (GI) toxicity and 15 (8.3%) experienced Grade ≥3 GU toxicity (21). Notably, this trial required a four-field box technique with margins up to 2 cm on the clinical target volume. Utilization of intensity-modulated radiation therapy, and even image-guided radiotherapy with fiducial marker placement, likely would have reduced the toxicity further. The Cancer and Leukemia Group B 99809 reported their long-term Phase II results from combination brachytherapy and EBRT with the addition of androgen deprivation therapy for intermediate-risk patients (22). With a median followup of over 6 years, the authors reported remarkable low rates of late Grade 3 toxicity (3% [95% confidence interval, 0–8%]). As there continue to be advances in imaging technology, there is a potential for additional improvements in intraoperative treatment planning and delivery to further improve outcomes.

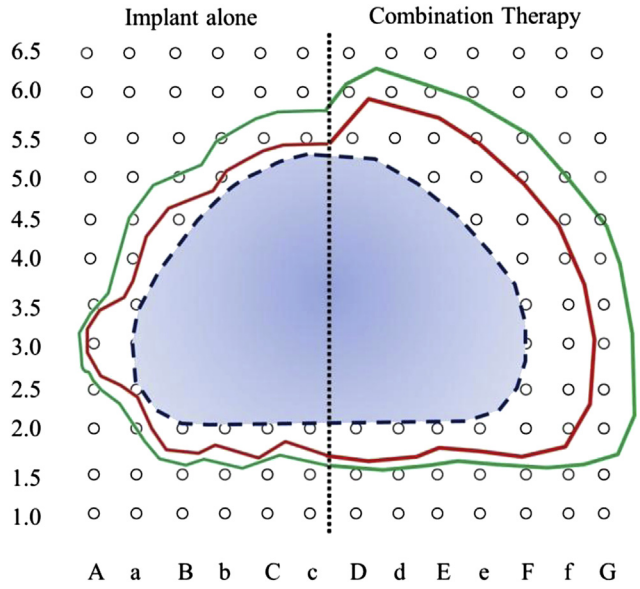

Fig. 1. Sample dosimetric comparison of implant alone to combination therapy. Example of dosimetric comparison of implant alone to combination therapy with EBRT and brachytherapy boost. Blue dashed line: prostate contour; red solid line: 100% isodose line; green solid line: 75% isodose line. Interval spacing between positions of 5 mm. EBRT = external beam radiation therapy.

It would be an overstatement to imply that all intermediate-risk patients require combination therapy. "Intermediate risk" comprises a heterogeneous group of patients with vastly different risks for failure (23). The current National Comprehensive Cancer Network risk grouping does not take into account important prognostic features such as percent positive biopsy cores (9), primary Gleason pattern (24), or prostate-specific antigen kinetics (25). For this reason, favorable intermediate-risk patients with low volume of disease and few intermediate-risk features may have adequate tumor control with a brachytherapy implant alone. However, patients with bulky disease or Gleason score 4 + 3 are at high risk of recurrence and extraprostatic extension and warrant more aggressive combination therapy.

Ultimately, the resolution of our point counterpoint debate will be addressed when the results of Radiation Therapy Oncology Group 0232 become available in the future. In this trial composed of intermediate-risk men treated with brachytherapy, patients are randomized to the addition of supplemental EBRT. This trial primarily includes favorable intermediate-risk patients and will provide Level 1 evidence to evaluate the effect of increased BED and improved extraprostatic coverage on tumor control prospectively. Until these results are known, the current data support the advantages of supplemental EBRT for intermediate-risk patients.

References

[1] Kuban DA, Tucker SL, Dang L, *et al*. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:67–74.
[2] Peeters ST, Heemberger WD, Roper PC, *et al*. Dose-response in radiotherapy for localized prostate cancer: Results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 2006;2:1990–1996.
[3] Dearnaley DP, Sydes MR, Graham JD, *et al*. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: First results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007; 8:475–487.
[4] Zietman AL, Bae K, Slater JD, *et al*. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: Long-term results from Proton Radiation Oncology Group/American College of Radiology 95-09. *J Clin Oncol* 2010;28:1106–1111.
[5] Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: A meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys* 2009;74:1405–1418.

[6] Sathya JR, Daris IR, Julian JA, *et al*. Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. *J Clin Oncol* 2005;23:1192–1199.
[7] Hoskin PJ, Motohashi K, Bownes P, *et al*. High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: Initial results of a randomised phase three trial. *Radiother Oncol* 2007;84:114–120.
[8] Levegrun S, Jackson A, Zelefsky MJ, *et al*. Risk group dependence of dose-response for biopsy outcome after three-dimensional conformal radiation therapy of prostate cancer. *Radiother Oncol* 2002;63: 11–26.
[9] Spratt DE, Pei X, Yamada Y, *et al*. Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2013;85: 686–692.
[10] Zumsteg ZS, Spratt DE, Pei X, *et al*. Short-term androgen-deprivation therapy improves prostate cancer-specific mortality in intermediate-risk prostate cancer patients undergoing dose-escalated external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 2013;85:1012–1017.
[11] Jones CU, Hunt D, McGowan DJ, *et al*. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med* 2011;365:107–118.
[12] Zelefsky MJ, Reuter VE, Fuks Z, *et al*. Influence of local tumor control on distant metastases and cancer related mortality after external beam radiotherapy for prostate cancer. *J Urol* 2008;179: 1368–1373. discussion 1373.
[13] Stock RG, Stone NN, Cesaretti JA, *et al*. Biologically effective dose values for prostate brachytherapy: Effects on PSA failure and post-treatment biopsy results. *Int J Radiat Oncol Biol Phys* 2006;64: 527–533.
[14] Stone NN, Stock RG, Cesaretti JA, *et al*. Local control following permanent prostate brachytherapy: Effect of high biologically effective dose on biopsy results and oncologic outcomes. *Int J Radiat Oncol Biol Phys* 2010;76:355–360.
[15] Roach M 3rd, Chen A, Song J, *et al*. Pretreatment prostate-specific antigen and Gleason score predict the risk of extracapsular extension and the risk of failure following radiotherapy in patients with clinically localized prostate cancer. *Semin Urol Oncol* 2000;18: 108–114.
[16] Theodorescu D, Frierson HF Jr, Sikes RA. Molecular determination of surgical margins using fossa biopsies at radical prostatectomy. *J Urol* 1999;161:1442–1448.
[17] Davis BJ, Pisansky TM, Wilson TM, *et al*. The radial distance of extraprostatic extension of prostate carcinoma: Implications for prostate brachytherapy. *Cancer* 1999;85:2630–2637.
[18] Sohayda C, Kupelian PA, Levin HS, *et al*. Extent of extracapsular extension in localized prostate cancer. *Urology* 2000;55:382–386.
[19] Merrick GS, Butler WM, Wallner KE, *et al*. Extracapsular radiation dose distribution after permanent prostate brachytherapy. *Am J Clin Oncol* 2003;26:e178–e189.
[20] Hoskin PJ, Rojas AM, Bownes PJ, *et al*. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol* 2012; 103:217–222.
[21] Lawton CA, Yan Y, Lee WR, *et al*. Long-term results of an RTOG Phase II trial (00-19) of external-beam radiation therapy combined with permanent source brachytherapy for intermediate-risk clinically localized adenocarcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2012;82:e795–e801.
[22] Hurwitz MD, Halabi S, Archer L, *et al*. Combination external beam radiation and brachytherapy boost with androgen deprivation for treatment of intermediate-risk prostate cancer: Long-term results of CALGB 99809. *Cancer* 2011;117:5579–5588.
[23] Zumsteg ZS, Spratt DE, Pei X, *et al*. A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. *Eur Urol* 2013. E-pub ahead of print.
[24] Spratt DE, Zumsteg Z, Ghadjar P, *et al*. Prognostic importance of Gleason 7 disease among patients treated with external beam radiation therapy for prostate cancer: Results of a detailed biopsy core analysis. *Int J Radiat Oncol Biol Phys* 2013;85:1254–1261.
[25] D'Amico AV, Chen MH, Roehl KA, *et al*. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. *N Engl J Med* 2004;351:125–135.
[26] Hinnen KA, Battermann JJ, van Roesmund JF, *et al*. Long-term biochemical and survival outcome of 921 patients treated with I-125 permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2010;76:1433–1438.
[27] Klein EA, Ciezki J, Kupelian PA, *et al*. Outcomes for intermediate risk prostate cancer: Are there advantages for surgery, external radiation, or brachytherapy? *Urol Oncol* 2009;27:67–71.
[28] Munro NP, Al-Qaisieh B, Bownes P, *et al*. Outcomes from Gleason 7, intermediate risk, localized prostate cancer treated with Iodine-125 monotherapy over 10 years. *Radiother Oncol* 2010;96:34–37.
[29] Taira AV, Merrick GS, Galbreath RW, *et al*. Natural history of clinically staged low- and intermediate-risk prostate cancer treated with monotherapeutic permanent interstitial brachytherapy. *Int J Radiat Oncol Biol Phys* 2010;76:349–354.
[30] Vassil AD, Murphy ES, Reddy CA, *et al*. Five year biochemical recurrence free survival for intermediate risk prostate cancer after radical prostatectomy, external beam radiation therapy or permanent seed implantation. *Urology* 2010;76:1251–1257.
[31] Zelefsky MJ, Kuban DA, Levy LB, *et al*. Multi-institutional analysis of long-term outcome for stages T1–T2 prostate cancer treated with permanent seed implantation. *Int J Radiat Oncol Biol Phys* 2007;67: 327–333.
[32] Ho AY, Burri RJ, Cesaretti JA, *et al*. Radiation dose predicts for biochemical control in intermediate-risk prostate cancer patients treated with low-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys* 2009;75:16–22.
[33] Critz FA, Levinson K. 10-Year disease-free survival rates after simultaneous irradiation for prostate cancer with a focus on calculation methodology. *J Urol* 2004;172(6 Pt 1):2232–2238.
[34] Dattoli M, Wallner K, True L, *et al*. Long-term outcomes after treatment with brachytherapy and supplemental conformal radiation for prostate cancer patients having intermediate and high-risk features. *Cancer* 2007;110:551–555.
[35] Merrick GS, Butler WM, Wallner KE, *et al*. Androgen-deprivation therapy does not impact cause-specific or overall survival after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2006;65:669–677.
[36] Bittner N, Merrick GS, Galbreath RW, *et al*. Primary causes of death after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2008;72:433–440.
[37] Burri RJ, Stone NN, Unger P, *et al*. Young men have equivalent biochemical outcomes compared with older men after treatment with brachytherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2010; 77:1315–1321.
[38] Merrick GS, Butler WM, Wallner KE, *et al*. Prognostic significance of perineural invasion on biochemical progression-free survival after prostate brachytherapy. *Urology* 2005;66:1048–1053.
[39] Potters L, Morgenstern C, Calugaru E, *et al*. 12-Year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. *J Urol* 2005;173:1562–1566.
[40] Zelefsky MJ, Chou JF, Pei X, *et al*. Predicting biochemical tumor control after brachytherapy for clinically localized prostate cancer: The Memorial Sloan-Kettering Cancer Center experience. *Brachytherapy* 2012;11:245–249.